REMARKS:

Claims 1-5 and 8-46 were pending in the instant application. Claims 1-5 were withdrawn from consideration. Claims 8-46 were under examination.

Claims 8, 15, and 16 have been amended. Support for the amendment can be found in the specification as originally filed at page 3, paragraph 8.

Claims 9, 12, 29, 39 have been amended to correct typographical errors.

Claim 11, 19, and 20 have been amended. Support for these amendments can be found in the specification as originally filed at p 4, ¶ 0011; p. 7, ¶ 0016; p. 37, ¶ 00112, p 5, ¶ 0013; p. 31, ¶ 0096; p. 17, ¶ 0039.

Claim 28 has been amended. Support for the amendment to claim 28 can be found in the specification as originally filed at, *e.g.*, p. 6, paragraph 14.

Claims 29 and 44 have been amended to correct their respective dependencies.

New claim 53 has been added. Support for new claim 53 can be found in the specification as originally filed, *e.g.*, at p. 18, ¶41.

New claim 54 has been added. Support for new claim 54 can be found in the specification as originally filed, *e.g.*, at p. 46, ¶132 and p. 77, ¶198.

No new matter has been introduced. Claims 1-5, 8-46, and 53-54 will be pending upon entry of the present remarks.

REVOCATION AND POWER OF ATTORNEY AND CORRESPONDENCE ADDRESS

Applicants submit herewith a Revocation and Power of Attorney on behalf of The Kenneth S. Warren Institute, Inc., the assignee of the entire right, title and interest in the above-identified patent application. Applicants request that the Revocation and Power of Attorney be made of record in the file history of the above-identified patent application. The assignment from the inventors to The Kenneth S. Warren Institute, Inc. is submitted concurrently herewith for recordation. A copy of the assignment is also enclosed.

Applicants also submit herewith a Change Of Correspondence Address Form PTO/SB/122 and request that all future correspondence be sent to the new address.

DOCKET NUMBER

Applicants request that the Patent Office revise its records to reflect the new Attorney docket number: 10165-037-999.

THE CLAIM OBJECTION TO CLAIM 39 SHOULD BE WITHDRAWN

The Examiner objected to claim 39 because claim 39 recited the plural of the word "methods." Applicants amended claim 39 to recite the singular "method." Applicants respectfully request that the Examiner withdraw this objection.

THE OBJECTION TO THE SPECIFICATION SHOULD BE WITHDRAWN

The Examiner objected to the specification because of the lack of capitalization of several trademarks and an underlined portion without any text. Applicants amended the specification to capitalize these trademarks and to delete the underlined portion.

Applicants respectfully request that the Examiner withdraw this objection.

THE PRIORITY

The above-identified application is the national stage of International Application No. PCT/US2003/021350 filed July 3, 2003, which claims benefit of priority from U.S. Application No. 10/188,905 filed July 3, 2002. The Examiner granted the international filing date of July 3, 2003 as the priority date.

Applicants have addressed the prior art-based rejections by the Examiner on their merits below. The claimed invention is patentable over the cited art independent from whether or not Applicants are entitled to the July 3, 2002 priority date.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT, SHOULD BE WITHDRAWN

Claims 8-46 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner contends that the specification does not reasonably provide enablement for a method of treating inflammation in a mammal comprising administering a generic tissue protective cytokine, a pharmaceutically acceptable

carrier and one or more anti-inflammatory agents or immunomodulatory agents.

Applicants assert that the specification is enabling for the claimed invention and that the indicated claims should be allowed.

The Legal Standard

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). In fact, well known subject matter is preferably omitted. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."). Further, one skilled in the art is presumed to use the information available to him in attempting to make or use the claimed invention. See *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation."). These enablement rules preclude the need for the patent applicant to "set forth every minute detail regarding the invention." *Phillips Petroleum Co. v. United States Steel Corp.*, 673 F. Supp. 1278, 1291 (D. Del. 1991); see also *DeGeorge v. Bernier*, 768 F.2d 1318, 1323 (Fed. Cir. 1985).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 USPQ 276, 279 (CCPA 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved; the guidance provided by the specification; the presence of working examples; the amount of pertinent literature; and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, so long as it is merely routine. *Id.*

Further, while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically

cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (CCPA 1976), at 218-219:

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, ... then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act. *Id.* at 219.

Thus, all that is required is a reasonable amount of guidance with respect to the direction of the experimentation; reasonable certainty with regard to the outcome of the experimentation is not required.

In addition, the Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of non-enablement. *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A. 1971); M.P.E.P. § 2164.02. A patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless there is reason to doubt the objective truth of the teachings which must be relied on for enabling support. *Id.*

Claims 8-46 Are Enabled

For the following reasons, claims 8-46 are enabled, and the rejections under 35 U.S.C. § 112, first paragraph, enablement, should be withdrawn.

(1) No undue experimentation is required to make the chemically modified erythropoietins for use in the claimed methods

The as-filed specification teaches that "tissue protective cytokines" include erythropoietin molecules that have been altered by at least one chemical modification (see, *e.g.*, p. 4, *l.* 15 to p. 5, *l.* 1; see also, *e.g.*, p. 16, *ll.* 10-23). A person skilled in the art could make and use the required chemically modified EPOs by using routine methods of chemical modification and by identifying suitable chemically modified EPOs using, *e.g.*, the assays disclosed in the present application.

The chemical structures of the chemically modified EPO molecules of the present invention are readily ascertainable by one of ordinary skill in light of the known structure of

EPO and the specific, routine chemical modifications described, *e.g.*, in Examples 2 and 3 of the as-filed specification (pages 89-100). The structure of native EPO is described in the specification, *e.g.*, at page 25, line 20 to page 26, line 1, and was also known in the art (*see, e.g.,* U.S. Patent No. 5,457,089 to Fibi *et al.* ("Fibi"), describing EPO at col. 1, ll. 14-19; Fibi is referenced in the present application at page 2, line 3. Moreover, the present specification provides: (1) examples of specific chemical sites on EPO that can be chemically modified to obtain chemically modified EPOs for use in the present invention; (2) methods for chemically modifying EPO to obtain chemically modified EPOs for use in the present invention; and (3) specific examples of chemically modified EPOs for use in the present invention.

Specific examples of sites for chemical modification on EPO molecules are provided, *e.g.*, at p. 14, *ll.* 10-23, and include, *e.g.*, arginine residues, lysine residues, tyrosine residues, glutamic acid residues and tryptophan residues. Additional examples of sites for chemical modifications of EPO molecules are detailed, *e.g.*, from p. 30, *l.* 21 to p. 38, *l.* 9.

Examples of methods for chemically modifying the EPO molecule, such as "guanidation, amidination, carbamylation (carbamoylation), trinitrophenylation, acetylation, succinylation, nitration," among others, are provided, *e.g.*, at p. 29, *ll.* 11-21. These and other examples of methods for chemically modifying the EPO molecule are described in detail, *e.g.*, at page 32, line 21 to page 38, line 9. For instance, desialylation, a specific method for chemically modifying EPO, is described, *e.g.*, at page 30, line 21 to page 31, line 6.

Methods for obtaining the required chemical modifications were also well-known in the art. For example, numerous examples of methods for modifying specific amino acid residues of proteins are described throughout the book Chemical Reagents for Protein Modification, authored by R. L. Lundblad (CRC Press: Boca Raton, Florida, 1991) ("Lundblad"). For instance, Chapters 6 and 7 describe methods of modifying cysteine residues and cleaving disulfide bonds; Chapter 10 describes methods of chemically modifying lysine residues of a protein; Chapter 11 describes methods of chemically modifying arginine residues of a protein; and Chapter 12 describes methods of chemically modifying tryptophan residues of a protein. Each of these methods of chemical modifications to proteins were within the ability of one skilled in the art at the time the application was filed. Copies of the title page, table of contents, and a representative chapter (Chapter 7, entitled "The Modification of Cysteine – Cleavage of Disulfide Bonds) from Lundblad are attached hereto as Exhibit A for the Examiner's convenience. If requested, Applicants can provide copies of additional content from Lundblad.

Moreover, numerous examples of particular chemically modified EPOs are provided throughout the specification. For instance, examples of particular chemically modified EPOs are provided, *e.g.*, at p. 7, *ll.* 6-15 and from p. 18, *l.* 15 to p. 19, *l.* 16. Examples of compound groups of chemically modified EPOs include, *e.g.*, carbamylated EPOs, succinylated EPOs, acetylated EPOs, biotinylated EPOs, iodinated EPOs and carboxymethyllysyl EPOs, as provided, *e.g.*, at p. 39, *l.* 1 to p. 41, *l.* 21. The specification further provides specific examples of compounds for each example compound group. *Id.* Chemical methods for obtaining these modifications were well-known in the art, as indicated, *e.g.*, by references cited in connection with the particular methods of chemical modification described in Examples 2 and 3 of the specification (pages 89-100).

In addition to the teachings detailed in the specification, other methods of chemically modifying EPO were also known to a person of ordinary skill at the time the application was filed. For example, WO 94/24160 to Boissel et al. ("Boissel") illustrates numerous methods of modifying EPO to obtain chemically modified EPOs. Importantly, however, Boissel is concerned with monitoring the effects of such chemical modification on EPO's "biological activity," by which Boissel means erythropoietic activity. (*See*, *e.g.*, Boissel at page 1, lines 19-21: "In terms of biological function, EPO has been recognized as the hematopoietic cytokine that regulates the process of red blood cell production, known as erythropoiesis.") By contrast, the present invention relates to, *inter alia*, administration of a chemically modified EPO as part of a method for treating inflammation (see, *e.g.*, claim 8). The methods described in Boissel for chemically modifying EPO serve as an illustration that the level of skill in the art at the time the present application was filed enabled one of ordinary skill to make the chemically modified EPOs for use in the present invention. Moreover, as discussed *infra*, a person of ordinary skill in the art could use the assays described in the specification and known in the art to test particular chemically modified EPOs for their suitability for use in the presently claimed invention.

(2) No undue experimentation is required to identify suitable chemically modified EPOs for use in the claimed methods

The claims are also rejected because "[i]t would be unpredictable for one of skill in the art to determine whether the claimed method would have an anti-inflammatory effect on the cells, tissue and/or organs of different mammals ..." (Office Action of March 28, 2007, at p. 11, *ll.* 7-9). According to *In re Angstadt*, however, "the unpredictability of the result of an

experiment is not a basis to conclude that the amount of experimentation is undue" 190 USPQ 214 (CCPA 1976), at 218-219. The specification provides results from *in vivo* and *in vitro* studies that describe and demonstrate assays that one of skill in the art could use to test a particular chemically modified EPO for its anti-inflammatory effect (see, e.g., Example 12, pages 110-115). While the outcome of a particular assay may not be known *ex ante*, this is not a grounds for concluding that the experimentation is undue because performing these assays requires merely routine experimentation.

(a) ASSAYS FOR ANTI-INFLAMMATORY EFFECT

Suitable combinations of a tissue protective cytokine and an anti-inflammatory agent can be tested in well-established models for inflammation. Such models include the experimental allergic encephalomyelitis model in rats (also known as experimental autoimmune encephalomyelitis) as disclosed in the present specification beginning at page 112, ¶318. At the time the application was filed, the performance of these assays was routine and did not require more than ordinary skill.

Additional models for inflammatory conditions are disclosed in the specification. In Example 12, beginning at p. 110, a middle cerebral artery occlusion model in rats is disclosed. Inflammatory activity can be measured in this model by, *e.g.*, leukocyte infiltration (p. 112, ¶315). An illustrative *in vitro* test is also provided in the specification at p. 114. Neuronal death-induced TNF production in neuron-glia cultures can be used as an assay system to test inflammatory responses, and therefore to test the anti-inflammatory effect of a compound of interest.

Further, blunt trauma was known to cause inflammatory responses that could be quantified, and therefore used as assay-systems for testing the anti-inflammatory effect of a compound (see, *e.g.*, Brines, p. 10529, rt. col.). Collagen-induced arthritis model in mice is another well-established model system for inflammatory activity. See, *e.g.*, Szabo *et al.*, 1998, PNAS 95(7):3867-72 (Exhibit G).

Simply because the outcome of a specific assay for each modified EPO may not be known in advance does not make the claimed methods non-enabled since unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue. See, *e.g.*, *Angstadt*.

(b) EVIDENCE OF ANTI-INFLAMMATORY EFFECT OF MODIFIED FORMS OF ERYTHROPOIETIN

Applicants submit herewith a copy of Savino *et al.*, 2006, Journal of Neuroimmunology 172:27-37 (Exhibit D; "Savino") to demonstrate that the two different chemically modified forms of EPO, namely carbamylated EPO and asialylated EPO ameliorate EAE.

Savino tested the effects of carbamylated EPO and asialoEPO in an EAE model. The present specification discloses carbamylated EPO at page 6, ¶14; asialoEPO is disclosed at p. 17, ¶37. Carbamylation of EPO was well-established as early as 1991 (see, p. 91, ¶237 of the present specification). A protocol for asialylating EPO is disclosed in the present specification at pp. 89-90, ¶¶233. The EAE model system is disclosed in the present specification at p. 112, ¶318 (see discussion above).

(c) EVIDENCE OF EPO's ANTI-INFLAMMATORY EFFECT IN OTHER MODEL SYSTEMS

Applicants submit herewith a copy of Cuzzocrea *et al.*, 2005, Arthritis & Rheumatism 52:940-950 ("Cuzzocrea;" Exhibit F). Cuzzocrea demonstrated that EPO exerts an anti-inflammatory effect in a collagen-induced arthritis model in mice. These data demonstrate that the anti-inflammatory effect of EPO is not limited to the EAE model.

(d) EVIDENCE OF SYNERGISTIC ANTI-INFLAMMATORY EFFECT

Applicants submit herewith a copy of Diem *et al.*, 2005, Brain 128:375-385 (Exhibit C; "Diem") to demonstrate that the combined administration of erythropoietin ("EPO") and an anti-inflammatory agent have synergistic effects (see, *e.g.*, p. 376 of Diem, last paragraph of the Introduction).

Diem tested the effects of EPO and the anti-inflammatory agent methylprednisolone ("MPred") alone or in combination in the experimental autoimmune encephalomyelitis ("EAE") model in rats (see discussion of the EAE model above). Diem found that the early administration of EPO combined with MPred therapy led to therapeutic effects that could not be obtained with EPO alone or with MPred alone.

A few especially compelling results will be discussed here. For example, Figure 1F shows a functional assay to demonstrate the synergistic effect of EPO and MPred together: Only the combined therapy of EPO and MPred restores visually evoked potentials in the visual cortex. Figure 4B demonstrates the synergistic effect of EPO and MPred in a structural assay: the combination of EPO and MPred significantly reduced the percentage of demyelination in the optic nerve. Thus, Diem demonstrates the synergistic effect of EPO together with MPred.

The EAE model is disclosed in the specification as originally filed starting at page 112, paragraph 317. It is noted that experimental autoimmune encephalomyelitis was previously referred to as experimental allergic encephalomyelitis. The use of MPred as an anti-inflammatory agent to be used in combination with EPO is disclosed in the present specification at p. 14, paragraph 30.

Thus, a later application of the combination therapy as taught in the present specification demonstrated the synergistic effect of the claimed therapy.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claims 8-46 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Claims 8-46 satisfy the written description requirement as discussed in detail below.

The Legal Standard

The test for sufficiency of written description is whether the disclosure of the application "reasonably conveys to the artisan that the inventor had possession" of the claimed subject matter. *In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. (BNA) 1089, 1096 (Fed. Cir. 1983); *accord Vas Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563; *see also, Ralston Purina Co. v. Far Mar Co, Inc.*, 772 F.2d 1570, 1575, 227 U.S.P.Q. (BNA) 177, 179 (Fed. Cir. 1985). The Court of Appeals for the Federal Circuit has repeatedly considered the written description requirement and consistently found that exacting detail is not necessary to meet the requirement:

If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, the adequate written description requirement is met. *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

The criteria for determining sufficiency of written description set forth in Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description Requirement" ("the Guidelines") (published in the January 5, 2001 Federal Register at Volume 66, Number 4, p. 1099-1111), specifies that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice (see (1)(a) above), reduction to drawings (see (1) (b) above), or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (see (1)(c), above). *Id.* at p. 1106, column 3, l. 13-29.

Where the specification discloses any relevant identifying characteristics, *i.e.*, physical, chemical and/or functional characteristics sufficient to allow a skilled artisan to recognize the applicant was in possession of the claimed invention, a rejection for lack of written description under Section 112, first paragraph, is misplaced. *Id.*

Claims 8-46 Satisfy the Written Description Requirement

The Examiner contends that the claims recite many different genera each of which encompass numerous species that are not further described (pp. 16-17 of the Office Action of March 28, 2007). These genera include: mammals comprising responsive cells, tissues, and/or organs; tissue-protective cytokines; anti-inflammatory agents; immuno-modulatory agents; anti-malarial agents; anti-viral agents; antibiotics; non-steroidal anti-inflammantory agents; anti-angiogenic agents, beta-agonists; proteinaceous agents; peptide mimetics; antibodies; nucleic acid molecules; small molecules; organic compounds; inorganic compounds; T-cell receptor modulators; cytokine receptor modulators; recombinantly produced erythropoietin; disease conditions; and traumas.

It is noted that what is conventional or well-known to one of skill in the art need not be disclosed in detail (Guidelines, at p. 1105, column 3, ll. 39-41), and, where the level of knowledge and skill in the art is high, a written description question should not be raised. *Id.*

at p. 1106, column 1, ll. 34-36. See also *Capon v. Eshhar*, 418 F.3d 1349, at 1357 (Fed. Cir. 2005).

Mammals Comprising Responsive Cells[1]

The genus of mammals is well-known in the art and numerous species of responsive cells are listed in the specification, at, *e.g.*, ¶8. A definition of responsive cells is provided at p. 26, ¶86.

Tissue-Protective Cytokines

Tissue-protective cytokines are described, *e.g.*, at p. 4, ¶11, of the specification. In particular, tissue-protective cytokines to be used with the methods of the invention include chemically modified forms of EPO. Numerous chemically modified forms of EPO are disclosed in the specification as discussed above.

Anti-Inflammatory Agents and Immuno-Modulatory Agents

Anti-inflammatory agents and immuno-modulatory agents were well-known in the art. Accordingly, it is not required to provide a listing of such agents with in the specification. Similarly, further specifications of anti-inflammatory agents and immuno-modulatory agents, such as, anti-malarial agents; anti-viral agents; antibiotics; non-steroidal anti-inflammantory agents; anti-angiogenic agents, beta-agonists; proteinaceous agents; peptide mimetics; antibodies; nucleic acid molecules; small molecules; organic compounds; inorganic compounds; T-cell receptor modulators; and cytokine receptor modulators, are well-known subgenera of anti-inflammatory agents and immuno-modulatory agents and need not explicitly be set forth in the specification.

Disease Conditions And Traumas

It is noted that the claims are limited to the treatment of inflammation. Accordingly, the recitation of "disease condition" and "trauma" in claim 43 are causes of the inflammation.

[1] The recitation "mammal comprising responsive cells, tissues, and/or organs" has been amended to "mammal comprising responsive cells."

Disease conditions and traumas that result in inflammation were also conventional known and therefore, need not be specifically recited in the patent application.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 8, 43, and 44 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that claim 44 recites inflammatory diseases although claim 44 purports to further specify the term "trauma."

In view of the amendment to claim 44, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, as being indefinite, should be withdrawn.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 8-16, 19-20, 28-29 and 43-46 have been rejected under 35 U.S.C. § 102 as being anticipated by Brines et al., Proc. Nat'l Acad. Sci. USA, 2000 Sept 12; 97(19):10526-10531 ("Brines").

The Legal Standard

The standard for an anticipatory reference is set forth in *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987): "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See also Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989)(holding that "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim"). "The elements must be arranged as required by the claim . . .." M.P.E.P. 2131.01. *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990).

The Claimed Invention Is Not Anticipated By Brines

Brines tested recombinant wild type human EPO in the EAE model and described the anti-inflammatory effect of EPO (p. 10530, lt. col.). Brines does *not* disclose the *combination* of EPO with an anti-inflammatory or immuno-modulatory agent. Thus, Brines

fails to teach the elements as arranged in the claims.

As Exhibit E, Applicants provide a copy of Brines annotated to indicate all occurrences of anti-inflammatory agents in the document. Nowhere does Brines teach or suggest using EPO in conjunction with an anti-inflammatory. In each case, Brines compares the activity of EPO to anti-inflammatory agents but does *not* propose combinations. A discussion of occurrence by occurrence in numerical order follows:

(1) (p. 10526, col. 1) For completeness, this recitation of "cytokine superfamily" has been included in this discussion. This occurrence merely mentions that EPO is a member of the cytokine superfamily, and provides background information on the expression pattern of EPO.

(2) (p. 10530, col. 1) Here, the authors of Brines state that treatment with glucocorticoids or IFN-beta (two anti-inflammatory agents) is typically followed by a "rebound" of symptoms. The authors also state their observation that such a rebound does not occur after treatment with EPO.

(3) and (4) (p. 10530, col. 2) Here, the authors simply use the term "cytokine" as a different word for EPO; "*the* cytokine" and "*this* cytokine" refer to EPO.

(5) (p. 10531, col. 2) Here, the authors simply state that cytokines other than EPO have immunomodulatory roles.

(6) (p. 10531, col. 2) Here the authors compare the action of EPO with other anti-inflammatory agents, such as glucocorticoids. Specifically, the authors describe that EPO acts in their EAE model in a manner consistent with known anti-inflammatory agents, such as glucocorticoids.

In summary, there is not a single place in Brines, where the authors mention or suggest that EPO should be combined with other anti-inflammatory agents or immunomodulatory agents. All the authors do is to compare the activity of EPO with the activity of other anti-inflammatory agents, such as glucocorticoids.

The claimed methods require the *combined* use of EPO and an anti-inflammatory agent or immunomodulatory agent for the treatment of inflammation, *i.e.*, the combination of these two agents is the required arrangement of the claim elements. Because Brines does not teach the combination of EPO with an anti-inflammatory agent or immunomodulatory agent, Brines fails to teach the claim elements as arranged in the claim, and Brines therefore does

not anticipate the presently claimed methods.

Claims 9-16, 19-20, 28-29, and 43-46 incorporate the limitations of claim 8 by virtue of their dependencies from claim 8. Accordingly, these dependent claims are also not anticipated by Brines.

Thus, the rejection of claims 8-16, 19-20, 28-29 and 43-46 under 35 U.S.C. § 102 as being anticipated by Brines should be withdrawn.

THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 8-46 have been rejected under 35 U.S.C. § 103 as being made obvious by Brines in view of Lin et al., U.S. Patent No. 5,621,080 ("Lin"), and Satake et al., Biochimica et Biophysica Acta. 1990; 1038: 125-129 ("Satake").

The Legal Standard

A finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and

claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue.* 127 S.Ct. at 1742, 82 USPQ at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* -- which are still good law post-*KSR* -- require that *both* the suggestion and the expectation of success must be found in the prior art, and not from knowledge gained from the applicant's disclosure.

In a post-*KSR* decision, the Federal Circuit stated:

> Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Takeda v. Alphapharm, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007). Thus, even post-*KSR* the prior art must teach a reason for the modification that would lead to the claimed invention.

Claims 8-46 Are Nonobvious and Should Be Allowed

As discussed above, Brines does not teach the combination of EPO with an anti-inflammatory agent or an immunomodulatory agent. Satake is concerned with modified

forms of EPO and their erythropoietic activity. Similarly, Lin is concerned with modified forms of recombinant EPO. Thus, neither Satake nor Lin even relates to treatment of inflammation.

The cited prior art does not make obvious the combination of EPO with an anti-inflammatory agent for the treatment of inflammation. Brines discloses the successful application of EPO in the EAE model of multiple sclerosis, an inflammatory condition. Brines compares the activity of EPO in that model with the use of anti-inflammatory agents and concludes EPO displays a manner of action consistent with other anti-inflammatory agents, such as glucocorticoids. See, occurrence (6) in Brines (Exhibit E).

Brines states that treatment with glucocorticoids or IFN-beta is typically followed by a "rebound" of symptoms. See, occurrence (2) in Brines (Exhibit E). In contrast, treatment with EPO is not followed by such a "rebound." *Id.*

Thus, in analogy to *Takeda*, there was no reason in the prior art that would have led the skilled artisan to modify the therapy using EPO by combining the EPO-therapy with an anti-inflammatory agent. On the contrary, the "rebound" effect observed with anti-inflammatory agents would have led away from combining EPO with an anti-inflammatory because the skilled artisan would have expected such a combination to trigger a "rebound."

Furthermore, because of the similar manner of action of anti-inflammatory agents and EPO (see occurrence (6) of Brines (Exhibit E)), the skilled artisan would not have expected synergism between EPO with an anti-inflammatory agent.

Claims 9-46 all depend directly or indirectly from claim 8, and thereby incorporate the limitations of claim 8. Because the independent claim 8 is not obvious as discussed above, the dependent claims 9-46 are also not obvious over the cited art.

Thus, the rejection of claims 8-46 under 35 U.S.C. § 103 over Brines in view of Lin and Satake should be withdrawn.

CONCLUSIONS:

Applicants respectfully request that the foregoing remarks and amendments be made of record in the file history of the instant application. Applicants estimate that the remarks and amendments made herein place the pending claims in condition for allowance.

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Respectfully submitted,

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